6694 *Organometallics* **2007,** *26,* 6694–6697

Preparation of Di-, Tri-, and Tetra-Substituted Functionalized Ferrocenes via Magnesium Organometallics

Armin H. Stoll, P. Mayer, and Paul Knochel*

Department of Chemistry and Biochemistry, Ludwig-Maximilians-University Munich, Butenandtstrasse 5-13, D-81377 Munich, Germany

Received October 18, 2007

Summary: Ferrocenyl carboxylic acid derivatives were metalated with TMPMgCl·LiCl, leading after reaction with electrophiles to 1,2-disubstituted ferrocenes. Further metalation of these disubstituted ferrocenes with TMPMgCl·LiCl afforded trisubstituted ferrocenes. A 1,2,3,4-tetrasubstituted ferrocene derivative could also be prepared in this way.

Since the discovery of ferrocene[1,2] in 1951, the preparation of functionalized ferrocene derivatives has been extensively studied,[3] especially with respect to applications in organic synthesis, asymmetric catalysis,[4,5] materials for nonlinear optics,[6] or bioorganometallic chemistry.[7] Various lithiation reactions[8,9] have been used for their preparation. Strong alkyllithium bases as well as sterically hindered lithium amides provide access to a number of polysubstituted ferrocene derivatives.[10] However, the high reactivity of lithioferrocenes usually precludes the presence of sensitive functional groups.[11] The magnesiation of unsubstituted ferrocene using TMP bases has also been described.[12] Herein, we wish to report the regioselective preparation of 1,2-, 1,2,3-, and 1,2,3,4-substituted ferrocenes bearing an ester, a nitrile, or a carboxylic acid by using TMPMgCl·LiCl[13] (magnesium 2,2,6,6-tetramethylpiperidide-lithium chloride) as a mixed Mg/Li amide. Thus, we have prepared several readily available ferrocenyl carbonyl compounds, **1a**−**d**, via lithiation reactions[10a,14] or esterification of the corresponding ferrocenecarbonyl chloride[15] (see Supporting Information). We have now found that treatment of ferrocenes of type **1** with TMPMgCl·LiCl (1.3 equiv, 0–10 °C) furnishes after a reaction time of 2.5–67 h regioselectively 2-magnesiated ferrocenes **2a**−**d** (Scheme 1). Their reactions with various electrophiles lead to 1,2-disubstituted ferrocenes.

Thus, the magnesiated esters **2a**,**b** provide after trapping with iodide (Table 1, entry 1) allyl bromide (entry 2), benzoyl chloride (entries 3 and 7), pivaldehyde (entries 4 and 6), ethyl chloroformate (entry 5), di-*tert*-butyl dicarbonate (entry 8), and the expected 1,2-disubstituted ferrocenes **3a** (60%), **3b** (72%), **3c** (70%), **3d** (60%), **3e** (67%), **3f** (82%), **3g** (80%), and **3h** (78%). The benzoylation reactions (entries 3 and 7) were performed by first transmetalation of **2a** or **2b** to the corresponding copper intermediates using CuCN·2LiCl[16] (1.3 equiv, −30 °C, 30 min). For the preparation of the 1,2-diester **3e**, the magnesiated ferrocene **2a** was transmetalated with $ZnCl_2$ (1.3 equiv, −30 °C, 30 min) before a carboxylation with $ClCO_2Et$ (1.5 equiv, 25 °C, 2.5 h) in the presence of $Pd(PPh_3)_4$ (1 mol %). A ferrocene bearing a cyano group such as **2c** was also smoothly magnesiated with TMPMgCl·LiCl (1.3 equiv, 0 °C, 67 h) and converted to the 1,2-disubstituted products **3i** (62%) and **3j** (75%) after the reaction with pivaldehyde (entry 9) and allyl bromide (entry 10). Interestingly, the magnesiation of the carboxylic acid **2d** was also successful by performing first a deprotonation with MeMgCl[17] (1.0 equiv, 10 °C, then room temperature, 30 min) followed by the addition of TMPMgCl·LiCl (1.3 equiv, 10 °C, 2.5 h). After trapping with allyl bromide the allylated carboxylic acid **3k** was obtained in 76% yield (entry 11).

This magnesiation procedure could also be extended to the preparation of new 1,2,3-trisubstituted and 1,2,3,4-tetrasubstituted ferrocenes. Thus, the treatment of the 1,2-diethyl ferrocenyl ester **3e** and the 1,2-di-*tert*-butyl ester **3h** with TMPMgCl·LiCl (1.1 equiv, 0 °C, 2 h, Scheme 2) afforded the magnesiated ferrocenes **4a** and **4b**. The quenching with various electrophiles such as chlorotrimethylstannane (Table 2, entry 1), allyl bromide

---

* Corresponding author. E-mail: paul.knochel@cup.uni-muenchen.de.

(1) Kealy, T. J.; Pauson, P. L. *Nature* **1951**, *168*, 1039.

(2) Miller, S. A.; Tebboth, J. A.; Tremaine, J. F. *J. Chem. Soc.* **1952**, 632.

(3) For a recent overview see: Togni, A.; Hayashi, T. *Ferrocenes*; VCH: Weinheim, Germany, 1995.

(4) Togni, A *Angew.Chem., Int. Ed. Engl.* **1996**, *35*, 1475.

(5) For a recent review see: Arrayás, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674.

(6) Long, N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 21.

(7) van Staveren, D. R.; Metzler-Nolte, N. *Chem. Rev.* **2004**, *104*, 5931.

(8) Benkeser, R. A.; Goggin, D.; Schroll, G. *J. Am. Chem. Soc.* **1954**, *76*, 4025.

(9) (a) Nesmeyanov, A. N.; Perevalova, E. G.; Golovnya, R. V.; Nesmeyanova, O. A. *Dokl. Akad. Nauk SSSR* **1955**, *97*, 459. (b) Nesmeyanov, A. N.; Perevalova, E. G.; Golovnya, R. V.; Shiovtseva, L. S. *Dokl. Akad. Nauk SSSR* **1955**, *102*, 535.

(10) (a) Rebiere, F.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1990**, *31*, 3121. (b) Enders, D.; Peters, R.; Lochtman, R.; Runsink, J. *Synlett* **1997**, 1462. (c) Balavoine, G. G. A.; Daran, J.-C.; Iftime, G.; Manoury, E.; Moreau-Bossuet, C. *J. Organomet. Chem.* **1998**, *567*, 191. (d) Miao, B.; Trinkl, M.; Snieckus, V. *Tetrahedron Lett.* **1999**, *40*, 2449. (e) Metallinos, C.; Snieckus, V. *Org. Lett.* **2002**, *4*, 1935. (f) Chiffre, J.; Coppel, Y.; Balavoine, G. G. A.; Daran, J.-C.; Manoury, E. *Organometallics* **2002**, *21*, 4552. (g) Peters, R.; Fischer, D. F. *Org. Lett.* **2005**, *7*, 4137. (h) Barley, H. R. L.; Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 6018. (i) Peters, R.; Xin, Z-q.; Fischer, D. F.; Schweizer, W. B. *Organometallics* **2006**, *25*, 2917. (j) Ivanov, V. V.; Hierso, J.-C.; Meunier, P. *Organometallics* **2006**, *25*, 989.

(11) Yus, M.; Foubelo, F. *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1, p 7.

(12) (a) Henderson, K. W.; Kennedy, A. R.; Mulvey, R. E.; O′Hara, C T.; Rowlings, R. B. *Chem. Commun.* **2001**, 1678. (b) Clegg, W.; Henderson, K. W.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T.; Rowlings, R. B.; Tooke, D. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3902. (c) Andrikopoulos, P. C.; Armstrong, D. R.; Clegg, W.; Gilfillan, C. J.; Hevia, E.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T.; Parkinson, J. A.; Tooke, D. M. *J. Am. Chem. Soc.* **2004**, *126*, 11612.

(13) (a) Krasovskiy, A; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681.

(14) (a) Ahn, K. H.; Cho, C.-W.; Beak, H.-H.; Park, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 4937. (b) Breit, B.; Breuninger, D. *Synthesis* **2005**, *16*, 2782.

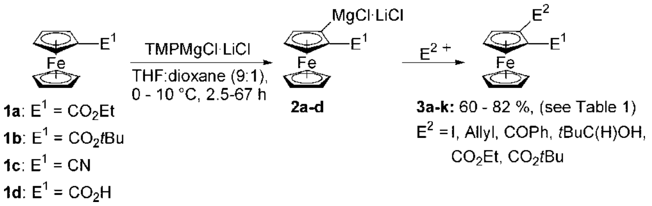
(15) Aguilar-Aguilar, A.; Allen, A. D.; Cabrera, E. P.; Fedorov, A.; Fu, N.; Henry-Riyad, H.; Leuninger, J.; Schmid, U.; Tidwell, T. T.; Verma, R. *J. Org. Chem.* **2005**, *70*, 9556.

(16) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(17) Kopp, F.; Wunderlich, S.; Knochel, P. *Chem. Commun.* **2007**, 2075.

10.1021/om701046c CCC: $37.00

Scheme 1. Regioselective Preparation of 1,2-Disubstituted Functionalized Ferrocene Derivatives Using TMPMgCl·LiCl



(entries 2 and 6), *N*,*N*-diethyl(methylene)immonium trifluoroacetate (entry 3), and ethyl cyanoformate (entries 4 and 7) provided the corresponding 1,2,3-trifunctionalized ferrocene derivatives **5a**−**f** in 34–50% yields.

Interestingly, the trisubstituted ferrocene **5d** could be magnesiated again with TMPMgCl·LiCl (1.1 equiv, −10 °C, 1 h), leading to the magnesium species **4c**. By the reaction with ethyl cyanoformate (0.9 equiv, −20 to 5 °C, 2 h) the ester **6** was obtained in 60% yield. The formation of the intermediate magnesiated reagents **4a**−**c** (Table 2, entries 1–7) was monitored by GC analysis of reaction aliquots quenched with a solution of iodide in THF, or alternatively with allyl bromide in the presence of CuCN·2LiCl.

Although the magnesiation of ferrocenes of type **3** proceeded well using TMPMgCl·LiCl, the resulting tri- and tetrasubstituted ferrocenes were found to be sensitive toward chromatographic purification (silica gel or Al_2O_3), leading to extensive decomposition. Furthermore, most of the polyfunctionalized ferrocenes proved also to be light sensitive. In order to get some structural information that would explain the instability of these ferrocenes, we have performed an X-ray structure analysis of the trisubstituted ferrocene **5d** (Figure 1) and the tetrasubstituted ferrocene **6** (Figure 2). The average Fe−C bond distances for the ferrocenes **5d** and **6** are very similar (2.03–2.04 Å), showing no especially weak η^5-binding. However, the corresponding cyclopentadienyl anions $(EtO_2C)_3C_5H_2^-$ and $(EtO_2C)_4C_5H^-$ should be highly stabilized anions.[18] Their formation may be the driving force of the ferrocene decomposition.

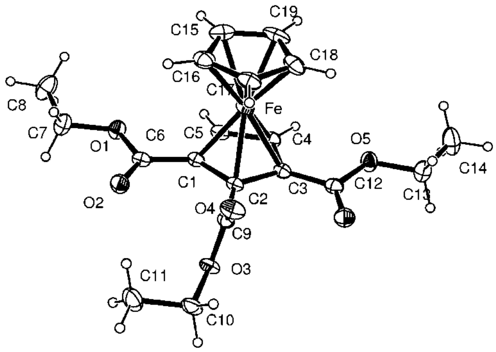


Figure 1. Molecular view of **5d** with atom-labeling scheme. Ellipsoids represent 30% probability.

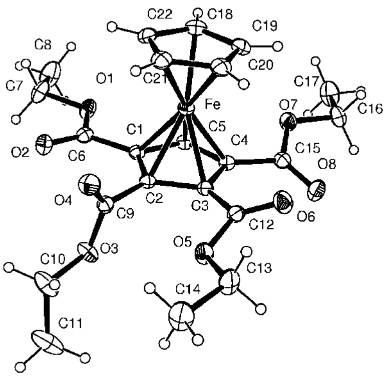
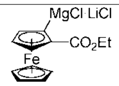
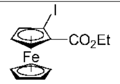
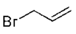
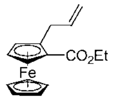
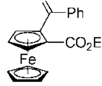
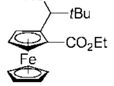
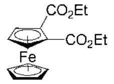
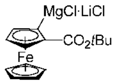
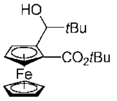
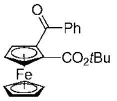
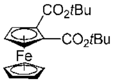
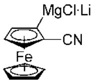
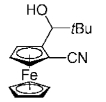
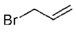
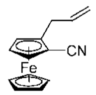
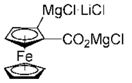
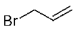
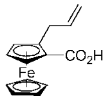


Figure 2. Molecular view of **6** with atom-labeling scheme. Ellipsoids represent 30% probability.

Table 1. Double Functionalized Ferrocene Derivatives of Type 3 Prepared by the Reaction of Magnesiated Ferrocene Derivatives of Type 2 and Various Electrophiles

Entry	Magnesiated ferrocene derivative		Electrophile	Product of type **3**		Yield(%)[a]
1		**2a**	I_2		**3a**	60
2		**2a**			**3b**	72[b]
3		**2a**	PhCOCl		**3c**	70[b]
4		**2a**	*t*BuCHO		**3d**	60
5		**2a**	ClCO₂Et		**3e**	67[c]
6		**2b**	*t*BuCHO		**3f**	82
7		**2b**	PhCOCl		**3g**	80[b]
8		**2b**	Boc₂O		**3h**	78
9		**2c**	*t*BuCHO		**3i**	62
10		**2c**			**3j**	75[b]
11		**2d**			**3k**	76[b]

a Isolated yield of analytically pure compound. [b] Reaction performed after the addition of catalytic or stoichiometric amounts of CuCN·2LiCl (0.1–1.3 equiv). [c] Reaction performed after the addition of $ZnCl_2$ (1.3 equiv, solution in THF) and $Pd(PPh_3)_4$ (1 mol %).

Scheme 2. Ester-Directed Magnesiation of 1,2- and 1,2,3-Substituted Ferrocenes 3e, 3h, and 5d Followed by Trapping with Electrophiles

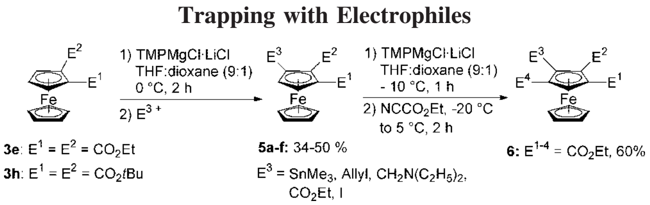
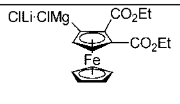
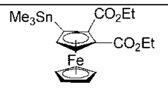
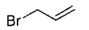
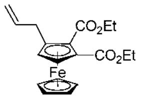
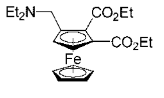
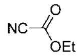
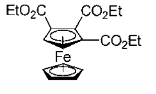
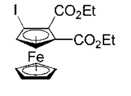
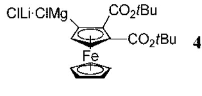
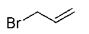
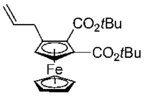
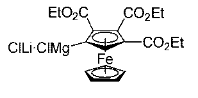
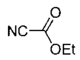
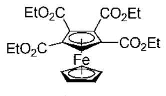


Table 2. Polyfunctionalized Ferrocene Derivatives of Type 5 and 6 by Successive Magnesiation and Trapping with Various Electrophiles

Entry	Magnesiated ferrocene derivative		Electrophile	Product of type **5**		Yield[a] (%)
1		**4a**	ClSnMe$_3$		**5a**	34
2	**4a**				**5b**	49[b]
3	**4a**		$Et_2\overset{+}{N}{=}CH_2\ \ \overset{-}{O}COCF_3$		**5c**	48
4	**4a**				**5d**	50
5	**4a**		I$_2$		**5e**	40
6		**4b**			**5f**	48[b]
7		**4c**			**6**	60

a Isolated yield of analytically pure compound. [b] Reaction performed after the addition of catalytic amounts of CuCN·2LiCl (0.1 equiv).

In summary, we have shown that the magnesiation of monosubstituted ferrocene derivatives with TMPMgCl·LiCl allows the regioselective preparation of various new polyfunctionalized ferrocenes bearing functional groups such as an ester, a nitrile, or a carboxylic acid. The mild reaction conditions and the versatile functional group tolerance of this method provide a useful complement to the well-known directed lithiation reaction,[10] opening a new way to the preparation of tri- and tetra-substituted ferrocenes.

Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere in dried glassware. All starting materials were purchased from commercial sources and used without further purification. Due to the light sensitivity of ferrocene derivatives, all reaction flasks were properly protected from light sources. Column chromatographies were also performed properly protected from light under a flow of nitrogen. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen before use. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR and capillary GC.

Preparation of the Reagent TMPMgCl·LiCl. A dry and argon-flushed 250 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly titrated *i*PrMgCl·LiCl[19] (100 mL, 1.2 M in THF, 120 mmol). 2,2,6,6-Tetramethylpiperidine (TMPH, 19.8 g, 126 mmol, 1.05 equiv) was added dropwise at room temperature. The reaction mixture was stirred at room temperature until gas evolution was completed (24−48 h).

General Procedure GP(A) for the Metalation of Monosubstituted Ferrocenes 1a,b. A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the ferrocene derivative **1a** or **1b** and dissolved in THF/dioxane (9:1). The reaction mixture was cooled to 10 °C, and TMPMgCl·LiCl (1.3 equiv, ca. 1.35 mol/L, solution in THF) was added dropwise. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I$_2$ in THF, or alternatively with allyl bromide in the presence of CuCN·2LiCl. After 2.5 h at 10 °C the neat electrophile (liquids) or its solution in THF (solids) was added at −30 °C. After 30 min, the cooling device was switched off, allowing the reaction mixture to warm slowly for 1−1.5 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with saturated aqueous NH$_4$Cl solution.

General Procedure GP(B) for the Metalation of Monosubstituted Ferrocene 1c. A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the ferrocene derivative **1c** and dissolved in THF/dioxane (9:1). The reaction mixture was cooled to 0 °C, and TMPMgCl·LiCl (1.3 equiv, ca. 1.35 mol/L, solution in THF) was added dropwise. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I$_2$ in THF, or alternatively with allyl bromide in the presence of CuCN·2LiCl. After 67 h at 0 °C the neat electrophile (liquids) or its solution in THF (solids) was added at −30 °C. After 30 min, the cooling device was removed, allowing the reaction mixture to warm to room temperature for 1 h. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with saturated aqueous NH$_4$Cl solution.

General Procedure GP(C) for the Metalation of 1,2-Disubtituted Ferrocenes 3e and 3h. A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the ferrocene derivative **3e** or **3h** and dissolved in THF/dioxane (9:1). The reaction mixture was cooled to 0 °C, and TMPMgCl·LiCl (1.1 equiv, ca. 1.35 mol/L, solution in THF) was added dropwise. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I$_2$ in THF, or alternatively with allyl bromide in the presence of CuCN·2LiCl. After 2 h at 0 °C, the neat electrophile (liquids) or its solution in THF (solids) was added at −30 °C. The completion of the reaction was checked by GC analysis of reaction aliquots quenched with saturated aqueous NH$_4$Cl solution.

Ethyl 2-Iodoferrocenecarboxylate (3a). According to GP(A), a solution of **1a** (258 mg, 1.0 mmol) in THF (0.9 mL) and dioxane (0.1 mL) was reacted with TMPMgCl·LiCl (0.95 mL, *c* = 1.37 mol/L) and iodide (0.33 g, 1.3 mmol). The reaction mixture was quenched with NH$_4$Cl$_{sat.}$ (25 mL) and H$_2$O (25 mL) and then extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic extracts were dried with Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluant: pentane/CH$_2$Cl$_2$, 2:1) and gave **3a** (229 mg, 60%) as a viscous, red-brown oil.

2-(1-Hydroxy-2,2-dimethylpropyl)ferrocenylnitrile (3i). According to GP(B), a solution of **1c** (211 mg, 1.0 mmol) in THF (0.9 mL) and dioxane (0.1 mL) was reacted with TMPMgCl·LiCl (0.96 mL, *c* = 1.35 mol/L) and pivaldehyde (78 mg, 0.9 mmol). The reaction mixture was quenched with NH$_4$Cl$_{sat.}$ (25 mL) and H$_2$O (25 mL) and then extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic extracts were dried with Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluant: pentane/diethyl ether, 4:1) and gave **3i** (165 mg, 62% based on used electrophile) as an orange solid.

Triethyl ferrocene-1,2,3-tricarboxylate (5d). According to GP(C), a solution of **3e** (165 mg, 0.5 mmol) in THF (0.45 mL) and dioxane (0.05 mL) was reacted with TMPMgCl·LiCl (0.41 mL, *c* = 1.34 mol/L) and ethyl cyanoformate (45 mg, 0.9 mmol).

---

(18) (a) Chambers, R. D.; Gray, W K; Vaughan, J. F. S.; Korn, S. R.; Medebielle, M.; Batsanov, A. S.; Lehmann, C. W.; Howard, J. A. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 135. (b) Laganis, E. D.; Lemal, D. M. *J. Am. Chem. Soc.* **1980**, *102*, 6633.

(19) *i*PrMgCl·LiCl is commercially available from Chemetall GmbH (Frankfurt am Main) and can be efficiently titrated by using I$_2$ in THF Procedure described in: Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890.

The reaction mixture was stirred for 1 h warming slowly from −30 to −20 °C. After removing the cooling device the mixture was stirred for 1 h at room temperature. Quenching with $NH_4Cl_{sat.}$ (25 mL) and H_2O (25 mL), extraction with Et_2O (3 × 40 mL), drying with Na_2SO_4, and concentration *in vacuo* afforded after purification by column chromatography (eluant: pentane/CH_2Cl_2, 2:1) **5d** (90 mg, 50%) as a dark brown solid.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (DFG), and Merck Research Laboratories (MSD) for financial support. We also thank Chemetall (Frankfurt) and BASF AG (Ludwigshafen) for the generous gift of chemicals.

Note Added after ASAP Publication. In the version of this paper that was published on the Web December 4, 2007, refs 10b and 10i were incorrect. The versions of these references that now appear are correct.

Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OM701046C